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The opinion in support of the decision being entered today (1) was not written for publication in a law journal and (2) is not binding precedent of the Board.

Paper No. 45

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte ROBERT G. PERGOLIZZI, SUSAN H. ERSTER
and W. TED BROWN

Appeal No. 95-3606
Application 07/827,691[1]

HEARD: May 3, 1999

Before GRON, TORCZON and LORIN, Administrative Patent Judges.

GRON, Administrative Patent Judge.

DECISION ON APPEAL UNDER 35 U.S.C. § 134

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[1] Application for patent filed January 28, 1992.

This is an appeal under 35 U.S.C. § 134 from an examiner's rejections of Claims 41, 10, 11, 15, 27, 6, 9, 34, 35, 42, and 29-33, all claims pending in this application.

Introduction

Claims 41, 10, 15, 27, 6, 9, 34, 35, 42, and 29-33 stand rejected under 35 U.S.C. § 103 as being unpatentable in view of the combined teachings of Kremer et al. (Kremer), "Mapping of DNA Instability at the Fragile X to a Trinucleotide Repeat Sequence p(CCG)$_n$," Science, Vol. 252, pp. 1711-1714 (June 1991), Innis (Innis I), U.S. 5,091,310, patented February 25, 1992 (prior art under 35 U.S.C. § 102(e) based on the application's filing date of September 23, 1988), and Innis et al. (Innis II), "PCR With 7-Deaza-2'-Deoxyguanosine Triphosphate," Chapter 7 of <u>PCR Protocols</u>, Innis et al., Ed., Academic Press, Inc., San Diego, Cal., pp. 54-59 (1990). Claim 11 stands rejected under 35 U.S.C. § 103 as being unpatentable in view of the combined teachings of Kremer, Innis I, Innis II, and Mullis et al. (Mullis), U.S. 4,965,188, patented October 23, 1990. The examiner acknowledged entry of applicants' Amendment Under 37 CFR §

1.193, filed June 23, 1995, in his Second Supplemental Examiner's Answer, mailed August 23, 1995. Claims 41 and 42 thereof are representative of the subject matter claimed and reproduced hereafter.

41. A method for ascertaining whether an individual is a carrier for, or afflicted with Fragile X comprising:

a) obtaining a nucleic acid sample from said individual selected from the group of nucleic acids consisting of DNA and RNA; and

b) amplifying a nucleic acid in said nucleic acid sample by performing a polymerase chain reaction in a reaction mixture that is substantially free of GTP and dGTP, said polymerase chain reaction comprising:

(1) at least one primer selected from the group consisting of oligonucleotides that are capable of hybridizing to sequences present in said sample within the FMR-1 fragile site, and oligonucleotides capable of hybridizing to sequences present in said sample that are sufficiently near the FMR-1 GC-rich fragile site to yield a detectable PCR product, and

(2) nucleotide analogue selected from the group consisting of 7-deaza GTP, inosine, and 7-deaza inosine; and

c) detecting the presence and size of said amplified nucleic acid by comparison with known standards, and using techniques known in the art; and

d) determining whether said individual is a carrier for, or afflicted with Fragile X.

42. A kit for determining whether an individual carries a mutation for Fragile X, comprising:

a) at least one oligonucleotide primer capable of hybridizing to nucleic acid sequences from an individual, wherein said sequences are selected from the group of sequences that consists of (I) sequences that are present within the FMR-1 fragile site, and (ii) sequences that are sufficiently near the FMR-1 GC-rich fragile site to yield a PCR product;

b) nucleotide analogue selected from the group consisting of 7-deaza GTP, inosine, and 7-deaza inosine; and

c) a PCR reaction mixture which is substantially free of added GTP or dGTP.

Discussion

1. Claim interpretation

Preliminarily, we note the following statement in the examiner's Second Supplemental Examiner's Answer (Sec. Suppl. Ans.), mailed August 23, 1995, page 3, second full paragraph, which reads:

> While Kremer does not explicitly teach combining the materials of the method together in a kit, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to package the materials together in the manner convenient for use to one of ordinary skill in the art.

In so stating, the examiner apparently concludes that the materials employed to perform the methods of Claims 41, 10, 11, 15, 27, 6, 9, 34, and 35 are identical in scope to the materials combined to form the kits of Claims 42 and 29 to 33. We hold that the scope of materials employed to perform the methods appellants claim is not commensurate with the scope of materials combined to form the kits appellants claim. Specifically, method step b) of Claim 41 reads in relevant part (emphasis added):

> b) amplifying a nucleic acid in said nucleic acid sample by performing a polymerase chain reaction in a reaction mixture that is substantially free of GTP <u>and</u> dGTP . . . .

In contrast, kit component c) of Claim 42 is (emphasis added):

> c) a PCR reaction mixture which is substantially free of added GTP <u>or</u> dGTP.

Thus, while the PCR reaction mixture of the method of Claim 41 must be "substantially free" of both GTP and dGTP, the reaction mixture included in the kit of Claim 42 need not be substantially free of both GTP and dGTP and can be used in methods outside the scope of Claim 41, which, though nonpreferred, applicants nevertheless regard as their invention. See applicants' specification (Spec.), page 19, lines 12-15; emphasis added):

> In addition to using an analogue of guanosine, it is further <u>preferred</u> that the method of the present invention

> is performed in a reaction mixture that is substantially free of both GTP and dGTP.

Next, the nucleotide analogues of method Claim 41 and kit Claim 42 are “selected from the group consisting of 7-deaza GTP, inosine, and 7-deaza inosine.” However, consistent with the teaching in the specification, we hold that the term “7-deaza GTP” in Claims 41 and 42 reads on both 7-deaza GTP and 7-deaza dGTP.[2] See the Specification (Spec., p. 19, l. 4-11; emphasis added):

> The process of the present invention uses an analogue of guanosine nucleotide. U.S. Patent No. 4,804,748 discloses analogues useful in the present invention and is hereby incorporated by reference. Preferred analogues include inosine, <u>7-deaza-guanosine</u> and 7-deaza inosine nucleotides (<u>both</u> ribo- <u>and deoxyribo-</u>). The 2'-deoxy analogues are more preferred and the 7-deaza-2'deoxy guanosine (7-deaza-2'-dGTP) analogue is further preferred.

Finally, we hold that the functional language, “for ascertaining whether an individual is a carrier for, or afflicted with Fragile X” in Claim 41, considered in conjunction with the “reaction mixture that is substantially free of GTP and dGTP” and in light of the supporting

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[2] A patent applicant may be his own lexicographer so long as he sets out his definition in the specification. <u>Intellicall, Inc. v. Phonometrics, Inc.</u>, 952 F.2d 1384, 1387-88, 21 USPQ2d 1383, 1386 (Fed. Cir. 1992).

specification, limits the scope of the claimed invention to reliable methods for ascertaining whether an individual is a carrier for, or afflicted with Fragile X. However, we hold that the language, “for determining whether an individual carries a mutation for Fragile X” in Claim 42, considered in conjunction with “a PCR reaction mixture which is substantially free of added GTP or dGTP” and in light of the specification, does not limit the scope of the subject matter claimed to kits comprising materials useful in reliable methods for determining whether an individual carries a mutation for Fragile X. In support of our holding that appellants’ Claim 41 is limited to reliable methods for ascertaining whether an individual is a carrier for, or afflicted with, Fragile X and that appellants’ Claim 42 is not limited to kits for use in performing reliable methods for determining whether an individual carries a mutation for Fragile X, we find in the specification teaching that the method of Claim 41 has substantial and practical utility while the kit of Claim 42 may or may not. See Cross v. Iizuka, 753 F.2d 1040, 1044, 224 USPQ 739, 742 (Fed. Cir. 1985):

> It is axiomatic that an invention cannot be considered

> "useful," in the sense that a patent can be granted on it, unless substantial or practical utility for the invention has been discovered and disclosed where such utility would not be obvious. *Brenner v. Manson*, 383 U.S. 519, ..., 148 USPQ 689 (1966).

Unlike the language of method Claim 41 and all claims dependent thereon, the language of kit Claim 42 and all claims dependent thereon reasonably may be interpreted consistent with the teaching in the specification, appellants' arguments, and the art made of record in this application to include materials for use in methods which cannot be used to reliably determine whether an individual carries a mutation for Fragile X. For example, see the results reported in applicants' Fig. 1, explained in Example 1 as follows (Spec., Example 1, p. 23, l. 12-24).

> DNA isolated from: (1) a normal individual (lanes 1); (2) a fragile X carrier male (lanes 2); (3) a male afflicted with the fragile X syndrome (lanes 3); and (4) a female fragile X carrier (lanes 4) were subjected to PCR in the presence of different proportions of 7-deaza-2'-dGTP to dGTP (100:0; 75:25; 50:50). The PCR products were analyzed by blot hybridization using a probe B (described above) complementary to the CGG repeat region of the FMR-1 locus. Figure 1 shows the results of this analysis. Note that the high molecular weight bands were detected only in the presence of 100% 7-deaza-2'-dGTP, 0% dGTP. In other words, the fully mutated fragile X gene was only detected when the PCR reaction mixture was substantially free of dGTP.

Claim language is to be given the broadest reasonable interpretation which is consistent with the invention described in the specification. In re Zletz, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989). The specification here clearly states that PCR reaction mixtures which are not substantially free of dGTP cannot reliably detect the fully mutated fragile X gene. In the kit of Claim 42, the PCR reaction mixtures need not be substantially free of dGTP.[3] Accordingly, we hold that the examiner erred in concluding that "Claim 42 is drawn to a kit having the reagents recited in the method of claim 41" (Sec. Suppl. Ans., p. 2, third para., last sentence).

2. Prior art teaching

A. Kremer

The examiner characterizes Kremer's disclosure and teachings as follows (Sec. Suppl. Ans., p. 3):

> Kremer teaches, in Figure 1B, amplification of a region of the FMR-1 gene, "PCR products spanning the p(CCG)n repeat [a GC rich region] were generated." Kremer also teaches using primers from the FMR-1 GC-rich fragile

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[3] In light of the teaching in the specification and the scope of method Claim 41, we surmise that applicants intended to limit the PCR reaction mixture in the kit of Claim 42 to a reaction mixture which is substantially free of GTP and dGTP.

site (see figure 1A, primers #203 and #213); detection by hybridization with a labeled CGG repeat probe (Kremer, p. 1713, Fig. 3, caption, see for example lines 18-22). Kremer discloses that size (or "number of base pairs") of a fragile X region is indicative of the fragile X genetic defect. "In addition, the repeat sequences exhibit instability and are generally larger in affected members of a pedigree than their unaffected carrier relatives . . ." (Kremer, page 1714, column 3, lines 11-14).

While Kremer does not explicitly teach combining the materials of the method together in a kit, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to package the materials together in a manner convenient for use to one of ordinary skill in the art.

The claims differ from Kremer in reciting the use of greater than 5 PCR cycles, a standard PCR buffer and use of 7-deaza-2'-GTP and in the absence of dGTP. . . .

Interestingly, in their Supplemental Reply To Examiner's Answer Under 37 C.F.R. § 1.193(b) filed September 15, 1995, or June 11, 1996, appellants do not respond to the examiner's characterization of Kremer' disclosure and teaching.

On close scrutiny, we find that the examiner too generally characterized Kremer's disclosure. Figure 1(A) depicts the

"DNA sequence of 1.03-kb Pst I fragment containing the $p(CCG)_n$ trinucleotide repeat" (Kremer, p. 1712, Fig. 1(A); emphasis added). Under Fig. 1(A), Kremer indicates (emphasis added):

For sequencing, the 1.03-kp Pst I restriction endonuclease

> fragment was isolated from pfxa1 and subcloned into the Pst I site in M13 mp18. . . . The 530-bp Nhe I to Pst I restriction endonucleases fragment was also isolated from pfxa1 and subcloned in both orientations into Xba 1-Pst I sites in M13 mp18 and 19. The difficulties in isolating M13 clones that spanned the p(CCG)$_n$ repeat in the reverse direction led us to use double-stranded sequencing of pfxa2 using oligodeoxyribonucleotide primers #201, 203, 204, 209, and 213. All sequencing was performed with Sanger's dideoxy method and with TAQuence sequencing kit (U.S. Biochemical Corp.). <u>Because of high CG content of the template DNA, samples were routinely prepared with 7-deaza-dGTP</u>, denatured in a final concentration of 50% formamide at 90^{0}C for 5 min. and loaded onto sequencing gels immediately without allowing to cool.

Under Fig. 1(B), Kremer teaches "PCR products spanning the p(CCG)$_n$ repeat were generated as described in the text and separated on a 1.5% low melting point argose (IBI) gel" (Kremer, p. 1712, Fig. 1(B)). Kremer describes PCR product generation in the text as follows (Kremer, pp. 1711-1712, bridging para.):

> In attempts to obtain sequence data for this region from normal individuals and additional fragile X genotype individuals, two approaches were undertaken. The first used two-stage PCR. Starting material was either total chromosomal DNA or, in one case, Eco RI-digested DNA from a normal individual; the DNA was fractionated by agarose gel electrophoresis to enrich for the 5-kb Eco RI fragment which contains the p(CCG)$_n$ repeat. In the first-stage

> PCR the 201 and 214 primers (Fig. 2) were utilized. The products of this reaction were used as template for the second-stage 203- and 213-primed PCR. The products of these reactions were then subcloned into M13 for sequence analysis. This analysis revealed that only the length of the repeat sequences varied--the flanking sequences between the PCR primers and the repeat remaining the same (Fig. 1B). In all cases the cloned PCR products were substantially shorter than anticipated, particularly since the fragile X individuals had large insertions or amplifications of sequences in this region . . . .

Fig. 3 is a “Southern blot analysis with fragile X-affected and normal males” (Kremer, p. 1713, Fig. 3):

> Total genomic DNA from lymphocytes was extracted and purified. A portion of each sample . . . was digested to completion with (**A**)Pvu II and Bam HI, (**B**) Pvu II and Nhe I, (**C**) Sau 3AI, (**D**) PST I and Rsa I. Lanes 1, 2, and 5 are from affected males. Lanes 3 and 4 are from normal males. Samples were separated by electrophoresis on a 1.3% agarose gel and transferred to Hybond N^+ blotting membrane (Amersham). The probe pfxa4 was ^{32}P-labeled by random priming and hybridized to the blots . . . and exposed to Xomat XK-1 film . . . .

On analysis, Kremer states (Kremer, p. 1713, col. 2, to p.1714, col. 1; emphasis added):

> We have concluded from all the experimental evidence that the unstable DNA sequence which characterizes the fragile X genotype maps to the $p(CCG)_n$ trinucleotide repeat. We have demonstrated that normal X chromosomes have about 40 $\pm$ 25 copies of $p(CCG)_n$ and that within these limits the sequence is a stable DNA polymorphism. The fragile X

genotype is characterized by an increased amount of unstable DNA that maps to the repeat. <u>Most of this unstable DNA and indeed most of the repeat in normal X chromosomes is lost during cloning and DNA amplification by PCR</u>, thus, its exact nature must remain speculative.

B. <u>Innis I and Innis II</u>

Innis I teaches that DNA amplification by PCR is useful to facilitate the cloning of DNA, characterization of both DNA and RNA sequences, and the detection of pathogens and disease states associated with the presence of particular DNA nucleic acid segments (Innis I, col. 1, l. 9-17). "PCR can be used in conjunction with labeled probes and 'dot-blot' methodology to detect the presence of a nucleic acid sequence initially present in extraordinarily small amounts" (Innis I, col. 1, l. 44-47). When inefficient or no amplification occurs by PCR, which unpredictably is often the case, extensive testing is often required to determine the source of the problem , e.g., the primers may be hybridizing to other regions of the target sequence (Innis I, col. 2, l. 34-50). It is Innis's intent to eliminate at least one potential problem, i.e., the formation and presence of secondary structure in the target DNA molecule which can greatly reduce the efficiency of amplification in the PCR process and interfere with normal gel migrations (Innis I, col. 3, l. 44-58). The problem Innis I confronts is most prevalent in nucleic acid sequences having high guanosine (G) and cytosine (C) content, i.e., sequences most likely to form Hoogsteen bonds (Innis I, col. 3, l. 51-54). Innis I proffers the following solution (Innis I, col. 4, l. 22-43):

> The utilization of c^7dGTP [(7-deaza-2'-deoxyguanosine-5'-triphosphate)] in a polymerase chain reaction results in the incorporation of 7-deazaguanine into the amplified DNA produced in the reaction. . . . 7-deazaguanine precludes Hoogsteen bond formation . . . [and] does not impair Watson-Crick base pairing as does inosine, another structure-destabilizing base analog. Utilization of inosine in PCR results in frequent mismatching of bases during primer extension.
>
> Utilization of c^7dGTP in PCR, however, results in an astounding increase in the specificity of PCR on nucleic acid templates that contain secondary structure and/or compressed regions.

Moreover, Innis I prefers to use c^7dGTP in combination with dGTP in the PCR reaction mixture for greatest efficiency (Innis I, col. 4, l. 38-43):

> PCR reactions performed with c^7dGTP but without dGTP are typically less efficient than PCR reaction performed with mixtures of c^7dGTP and dGTP. The optimum mixture is believed to be about 3:1 c^7dGTP and dGTP, respectively.

Innis II restates an earlier analysis of the problem and his solutions (Innis II, pp. 54-57), including an example of "PCR Using a 3:1 c^7dGTP:dGTP Mixture" (Innis II, p. 55). However, now Innis II states (Innis II, pp. 56 and 58, bridging para.):

> In our initial publication describing the use of c^7dGTP for structure-independent PCR (McConlogue et al. 1988), we pointed out that PCRs with c^7dGTP (or mixtures of c^7dGTP and dGTP) appeared to be less efficient on most templates than were PCRs with dGTP alone. This has now been shown to be incorrect. We have discovered that PCR products containing c^7dGTP simply do not stain efficiently with ethidium bromide, presumably because adjacent base stacking is diminished in the c^7dGTP-containing DNA. In fact, PCR (including asymmetric PCR) with c^7dGTP is as efficient as it is with dGTP for most templates, and for difficult templates, is vastly superior to PCR with dGTP alone. . . .
> Indeed, from these results it appears that the only reason to use a mixture of c^7dGTP and dGTP is that incorporation of some dGTP is necessary for visualization of the product by ethidium staining.

Innis II adds (Innis II, p. 58, last para.):

> We (McConlogue et al. 1988) also showed that DNA amplified in the presence of 100% c^7dGTP was cleavable by *Taq* I restriction endonuclease (T'CGA). At that time, we had not tried digesting c^7dGTP-amplified DNA with other restriction enzymes. In contrast, we show here that incorporation of c^7dGTP during PCR can interfere with subsequent digestion by some enzymes . . . . Under the conditions of approximately 20-fold overdigestion, about 95% of the dGTP-containing DNA was cleaved. In

> contrast, the c^7dGTP-containing DNA (a 3:1 mix with dGTP) was cleaved only 10 to 20% by *Eco*RI . . . and *Pst*I . . . and about 50% by *Hind*III . . . .

3. <u>*Prima facie* obviousness under 35 U.S.C. § 103</u>

The examiner has the initial burden to establish a *prima facie* case of obviousness under 35 U.S.C. § 103. <u>In re Fine</u>, 837 F.2d 1071, 1074, 5 USPQ 1596, 1598 (Fed. Cir. 1988); <u>In re Piasecki</u>, 745 F.2d 1468, 1472, 223 USPQ 785, 788 (Fed. Cir. 1984). The prior art references used to support *prima facie* obviousness must be read for everything they fairly would have taught a person having ordinary skill in the art. <u>In re Burckel</u>, 592 F.2d 1175, 1179, 201 USPQ 67, 70 (CCPA 1979); <u>In re Lamberti</u>, 545 F.2d 747, 750, 192 USPQ 278, 280 (CCPA 1976).

In that light, we revisit the references upon which the examiner relies. It is instructive first to study the Background of the Invention Innis I describes. Most especially, Innis I teaches (Innis II, col. 2, l. 51-65):

> Scientists working in areas not involving the polymerase chain reaction have observed that certain nucleic acid sequences can form stable secondary structures, such as palindromic hairpin loops or compressed regions. Because the presence of such structures can lead to anomalous migration patterns during gel electrophoresis, i.e., as in DNA sequencing, researchers attempted to find means for preventing the formation of secondary structures in nucleic acids.

> Barr et al., 1986, *Bio Techniques* 4(5):528-532, reported that use of 7-deaza-2'-deoxyguanosine-5'-triphosphate (c^7dGTP) in dideoxy-sequencing reaction mixtures helped to resolve abnormal and compressed regions in the sequencing gels.

From the above-quoted background described by Innis I, and the Innis I disclosure as a whole, we find that persons having ordinary skill in the art at the time this application was filed would have understood that dideoxy-sequencing processes do not necessarily involve the polymerase chain reaction and would have considered the use of c^7dGTP in dideoxy-sequencing to help resolve abnormal and compressed regions in the sequencing gels to be patentably distinct from the use of c^7dGTP in polymerase chain reaction mixtures for structure-independent DNA amplification. Accordingly, we hold that the examiner erred in liberally extracting bits and pieces from the description of each of the distinct processes described in Kremer with the hindsight purpose of reconstructing the process appellants claim. “It is impermissible . . . simply to engage in a hindsight reconstruction of the claimed invention, using the applicant’s structure as a template and selecting elements from references to fill the gaps.” In re Gorman, 933 F.2d 982, 987, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991). That the examiner engaged in hindsight reconstruction of the subject matter claimed is evident in this case because, while Kremer routinely used 7-deaza-dGTP when sequencing by Sanger's dideoxy method and with a TAQuence sequencing kit because of a high GC content of the template DNA (Kremer, p. 1712, Fig. 1. (**A**)), Kremer appears not to have considered the use of 7-deaza-dGTP in PCR analysis. See Figs. 2 and 3. Moreover, Kremer's attempts to determine the sequence of fragile X by PCR analysis appears to have been foiled by unstable DNA (Kremer, p. 1713, col. 3):

> The fragile X genotype is characterized by an increased amount of unstable DNA that maps to the repeat. Most of this unstable repeat and indeed most of the repeat in normal chromosomes is lost during cloning and DNA amplification by PCR; thus its exact nature must remain speculative.

Thus we find no teaching in Kremer, which would have led persons having ordinary skill in the art to reasonably expect success when amplifying unstable fragile X DNA by PCR with or without the addition of 7-deaza-dGTP to the PCR reaction mixture. Nevertheless, even if persons having ordinary skill in the art reasonably would have expected from the combined teachings of Kremer, Innis I, and Innis II that the process Innis I and Innis II describe would have been useful for amplifying unstable fragile X DNA from a nucleic acid sample by conventional PCR, detecting the presence and size of said amplified nucleic acid by comparison with known standards, and determining whether the individual source of the nucleic acid sample is a carrier for, or afflicted with fragile X, we find that the combination of Innis I and Innis II would not have led persons having ordinary skill in the art reasonably to expect to successfully perform PCR analysis for fragile X nucleic acid sequences using c^7dGTP substantially free of GTP and dGTP, compare the detection of the presence and size of said nucleic acid sequences by known techniques, and reliably determine whether the individual source of the nucleic acid sample is a carrier for, or afflicted with fragile X. Despite the examiner's portrayal of the teaching of Innis II, we find no less preference in Innis II for using a 3:1 c^7dGTP:dGTP mixture than is indicated in Innis I.

Innis II refers to PCR with c^7dGTP and PCR with c^7dGTP and dGTP in the alternative, i.e., "PCRs with c^7dGTP (or mixtures of c^7dGTP and dGTP)" (Innis II, p. 56, third line under Results and Discussion). Innis II admits to having previously erred in suggesting that "PCRs with c^7dGTP (or mixtures of c^7dGTP and dGTP) appeared to be less efficient on most templates than were PCRs with dGTP alone" (Innis II, p. 56, first five lines; emphasis added). In our view, Innis II neither expressly states nor reasonably suggests that PCRs with c^7dGTP are more efficient than PCRs with mixtures of c^7dGTP and dGTP. To the contrary, Innis II teaches that "PCR (including asymmetric PCR) with c^7dGTP is as efficient as it is with dGTP for most templates, and for difficult templates, is vastly superior to PCR with dGTP alone" (Innis II, p. 58, first full sentence) and proffers PCR with a 3:1 c^7dGTP: dGTP mixture as the preferred example of PCR with c^7dGTP (Innis II, p. 55). Moreover, Innis II provides good reasons why persons having ordinary skill in the art reasonably would have preferred to use a mixture of c^7dGTP and dGTP in a PCR reaction mixture over c^7dGTP substantially free of GTP and dGTP, (1) "dGTP is necessary for visualization of the product by ethidium staining" (Innis II, p. 58), and (2) "incorporation of c^7dGTP during PCR can interfere with subsequent digestion by some enzymes" (Innis II, last para., second sentence).

Accordingly, we find no motivation whatsoever in the combined prior art teachings, as a whole, to use c^7dGTP substantially free of GTP and dGTP during PCR over a 3:1

c^7dGTP:dGTP mixture in methods for ascertaining whether an individual is a carrier for, or afflicted with Fragile X. To the contrary, c^7dGTP:dGTP mixtures are preferred where, as here, the presence and size of the amplified nucleic acid is to be detected and compared with known standards using techniques known in the art (Claim 41, para. c)).

"The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in light
of the prior art." In re Dow Chemical Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). With regard to method of Claims 41, 10, 11, 15, 27, 6, 9, 34 and 35, the prior art on its face reasonably provides persons having ordinary skill in the art with neither the motivation to perform appellants' method for reliably ascertaining whether an individual is a carrier for, or afflicted with fragile X nor a reasonable likelihood of success. We need not further consider the evidence to which appellants point in rebuttal, because we hold that the combined teachings of Kremer, Innis I and Innis

II do not establish a *prima facie* case of unpatentability of Claim 41 under 35 U.S.C.
§ 103. It should suffice for this panel to merely point out that the examiner conceded during the course of his appearance at Oral Hearing on May 3, 1999 that c^7dGTP is expensive in comparison to dGTP and did not deny and has not denied that appellants' arguments that Fu et al. (Fu), "Variation of the CGG Repeat at the Fragile X Site Results in Genetic Instability: Resolution of the Sherman Paradox," Cell, Vol. 67, pp. 1047-1058 (December 20, 1991), and other extrinsic evidence of record, support a finding that Kremer, Innis I, and Innis II would not have led persons having ordinary skill in the art to carry out the process appellants claim with a reasonable likelihood of successfully performing the substantial and practical function it was designed to perform.

Kit claims 42 and 29-33 stand on a completely different footing. We hold that, unlike method Claim 41, the kit appellants claim merely comprises (Claim 42; emphasis added):

a) "at least one oligonucleotide primer capable of hybridizing to nucleic acid sequences present within or sufficiently near the FMR-1 GC-rich fragile site . . .";

b) "7-deaza GTP" (i.e., 7-deaza GTP or 7-deaza dGTP); and

c) “a PCR reaction mixture which is substantially free of added GTP <u>or</u> dGTP.”

In Fig. 1. (**A**), Kremer describes the following (Kremer, p. 1712):

> DNA sequence of 1.03-kb Pst I fragment containing the p(CCG)$_n$ trinucleotide repeat. . . . For sequencing, the 1.03-kp Pst I restriction endonuclease fragment was isolated from pfxa1 and subcloned into the Pst I site in M13 mp18. . . . The 530-bp Nhe I to Pst I restriction endonucleases fragment was also isolated from pfxa1 and subcloned in both orientations into Xba 1-Pst I sites in M13 mp18 and 19. The difficulties in isolating M13 clones that spanned the p(CCG)$_n$ repeat in the reverse direction led us to use double-stranded sequencing of pfxa2 using oligo-deoxyribonucleotide primers #201, 203, 204, 209, and 213. All sequencing was performed with Sanger’s dideoxy method and with TAQuence sequencing kit (U.S Biochemical Corp.). Because of high CG content of the template DNA, samples were routinely prepared with 7-deaza-dGTP, denatured in a final concentration of 50% formamide at 90^{o}C for 5 min. and loaded onto sequencing gels immediately without allowing to cool.

Based on Fig. 1 and Kremer’s teaching at column 1, paragraph bridging columns 1 and 2, to column 4, paragraph bridging columns 3 and 4, we find that Kremer describes a method for sequencing a 1.03-kb Pst I PCR DNA fragment containing the p(CCG)$_n$ fragile X trinucleotide repeat using at least one PCR primer capable of hybridizing to nucleic acid sequences present within or sufficiently near the FMR-1 GC-rich fragile site which are selected from the group consisting primers #201, 203, 204, 209, and 213, 7-deaza-dGTP because of the high GC-content of the template DNA, and Sanger’s dideoxy method and a TAQuence sequencing kit. We find that the PCR reaction mixture used for, and the PCR primers and 7-deaza-dGTP utilized in Kremer’s sequencing method all reasonably appear to be substantially free of added GTP or dGTP and together constitute a kit for use in DNA sequencing. Compare the findings on page 3 of the Second Supplemental Examiner’s Answer:

> Kremer teaches, in Figure 1B, amplification of a region of the FMR-1 gene, “PCR products spanning the p(CCG)n repeat [a GC rich region] were generated.” Kremer also teaches using primers from the FMR-1 GC-rich fragile site (see figure 1A, primers #203 and #213); detection by hybridization with a labeled CGG repeat probe (Kremer, p. 1713, Fig. 3, caption, see for example lines 18-22).

Moreover, we hold that the PCR reaction mixture of the kit of appellants’ Claim 42 may include GTP or dGTP and, accordingly, the preliminary functional language does not appear to further limit the claimed kit for the utility specified. Thus, since Innis I would have taught a person having ordinary skill in the art that 7-deaza-dGTP alone is useful for sequencing DNA having a high GC-content (Innis I, col. 2, l. 51-65) and Innis I and II teach that a 3:1 c^7dGTP:dGTP mixture is preferred for use in structure-independent DNA amplification by PCR at least when visualization of the product using known techniques is required, it would have been *prima facie* obvious to a person having ordinary skill in the art to use either 7-deaza-dGTP or 3:1 c^7dGTP:dGTP mixtures as the 7-deaza-dGTP additive routinely used in the fragile X DNA sequencing process described by Kremer. While Claim 42 is directed to "[a] kit for determining whether an individual carries a mutation for Fragile X," it is apparent from appellants' own specification that opening the PCR reaction mixture to added GTP or dGTP precludes reliable use of the full scope of the claimed kit for the determination indicated. Note that In re Dillon, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1990) (en banc), cert. denied, 500 U.S. 904 (1991), instructs at 693, 16 USPQ2d at 1901:

> Each situation must be considered on its own facts, but it is not necessary in order to establish a *prima facie* case of obviousness that both [the] . . . key component[s] of a composition . . . be shown and that there be a suggestion

> in or expectation from *the prior art* that the claimed . . . composition will have the same or a similar utility *as one newly discovered by applicant*. . . . In particular, the statement that a *prima facie* obviousness rejection is not supported if no reference shows or suggests the newly discovered properties and results of a claimed . . . [composition] is not the law.
>
> . . . The art provided the motivation to make the claimed compositions in the expectation that they would have similar properties.

Having determined that the subject matter of Claims 42 and 29-33 would have been *prima facie* obvious to a person having ordinary skill in the art for sequencing of DNA with high GC content in view of the combined teachings of Kremer, Innis I, and Innis II,[4] the burden to present evidence to the contrary shifted to appellants. In re Piasecki, 745 F.2d at 1472, 223 USPQ at 788. However, the evidence appellants have submitted in rebuttal emphasizes the kit's unexpected utility in methods for reliably "ascertaining whether an individual is a carrier for, or afflicted with Fragile X" (Claim 41). We restate our holding that the kit appellants claim is not limited for use in the method of Claim 41. See

[4] The examiner cited Kremer, Fig. 3, p. 1713, for its description to include labeled probes for Southern blot analysis of molecular size in addition to sequence analysis (Sec. Suppl. Ans., p. 3, first full para.).

our earlier claim interpretation. See In re Pearson, 494 F.2d 1399, 1403, 181 USPQ 641, 644 (CCPA 1974) (An old or obvious composition would not undergo a metamorphosis to a new or unobvious composition by labeling its container to show that the composition is suitable for another purpose.)

Accordingly, we reverse the examiner’s rejection of method Claims 41, 10, 15, 27, 6, 9, 34, and 35 under 35 U.S.C. § 103 in view of the combined teachings of Kremer, Innis I, and Innis II and the examiner’s rejection of method Claim 11 under 35 U.S.C.
§ 103 in view of the combined teachings of Kremer, Innis I, Innis II, and Mullis. However, we affirm the examiner’s rejection of Claims 42 and 29-33 under 35 U.S.C. § 103 in view of the combined teachings of Kremer, Innis I, and Innis II. While we affirm the examiner’s conclusion to reject Claims 42 and 29-33 in view of the combined teachings of Kremer, Innis I, and Innis II, we do so on the basis of new interpretations of the language and scope of the invention of Claim 42 and prior art teachings which either differ markedly from those of the examiner or were not specifically considered by the examiner. Accordingly, our affirmance of the examiner’s rejection of Claims 42 and 29-33 under 35 U.S.C. § 103 in view

of the combined teachings of Kremer, Innis I, and Innis II is a NEW GROUND OF REJECTION UNDER 37 CFR § 1.196(b).

Other Issues

The examiner has not considered the full scope of the subject matter claimed as we have interpreted it. Here, as in all cases, the examiner must determine what is being claimed before patentability under 35 U.S.C. § 102, or 103, or 112, first paragraph, can begin to be considered. As In re Moore, 439 F.2d 1232, 169 USPQ 236 (CCPA 1971), instructs at 1235, 169 USPQ at 238:

> [T]he claims must be analyzed first in order to determine exactly what subject matter they encompass. . . .
>
> The first inquiry therefore is merely to determine whether the claims do, in fact, set out and circumscribe a particular area with a reasonable degree of precision and particularity. It is here where the definiteness of the language employed must be analyzed--not in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art.

See also In re Wilder, 429 F.2d 447, 450, 166 USPQ 545, 548 (CCPA 1970)("Once having ascertained exactly what subject matter is being claimed, the next inquiry must be into whether such subject matter is novel."), and In re Geerdes, 491 F.2d 1260, 1262, 180 USPQ 789, 791 (CCPA 1974)("Before considering the rejections under 35 U.S.C. §§ 103 and 112, we must first decide . . . [what] the claims include within their scope.”)

For example, we have compared the prior art teaching to the claimed subject matter by interpreting the steps of Claim 41, i.e.:

> c) detecting the presence and size of said amplified nucleic acid by comparison with known standards, and using techniques known in the art; and
>
> d) determining whether said individual is a carrier for, or afflicted with Fragile X[;]

and the composition of the Claim 42 kit in a manner consistent with reliably “ascertaining whether an individual is a carrier for, or afflicted with Fragile X” (Claim 41) and the named parts of the kit of Claim 42. Our conclusions as to the patentability of appellants’ claimed methods and kits under 35 U.S.C. § 103, and under 35 U.S.C. § 102 as the epitome of obviousness, are limited thereby. However, the steps of Claim 41 appear to this panel to be so unclear and indefinite and overly broad that the examiner may wish to and correctly should reconsider the patentability of all claimed methods under the second and then first paragraphs of 35 U.S.C. § 112.

For example, given the phrase its broadest reasonable interpretation consistent with the description of the claimed method in the specification,[5] what scope should be attributed to the step of "c) detecting the presence and size of said amplified nucleic acid by comparison with known standards, and using techniques known in the art" (Claim 41; emphasis added). Moreover, we are uncertain as to
the intended meaning and scope of step "d) determining whether said individual is a carrier for, or afflicted with Fragile X" (Claim 41) in the context of Claim 41 which is drawn to a "method for ascertaining whether an individual is a carrier for, or afflicted with Fragile X comprising [the step of] . . . determining whether said individual is a carrier for, or afflicted with Fragile X."

Accordingly, we remand this application to the examiner to consider anew of the patentability of the claimed subject matter under 35 U.S.C. § 112, second paragraph, 35 U.S.C. § 112, first paragraph, and 35 U.S.C. § 103.

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[5] See In re Zletz, 893 F.2d at 321, 13 USPQ2d at 1320.

Conclusion

We reverse the examiner’s rejection of method Claims 41, 10, 15, 27, 6, 9, 34, and 35 under 35 U.S.C. § 103 in view of the combined teachings of Kremer, Innis I, and Innis II.

We reverse the examiner’s rejection of method Claim 11 under 35 U.S.C. § 103 in view of the combined teachings of Kremer, Innis I, Innis II, and Mullis.

We affirm the examiner’s rejection of Claims 42 and 29-33 under 35 U.S.C. § 103 in view of the combined teachings of Kremer, Innis I, and Innis II. This rejection constitutes a NEW GROUND OF REJECTION UNDER 37 CFR § 1.196(b).

We remand this application to the examiner for consideration anew of the patentability of the claimed subject matter under 35 U.S.C. § 112, second paragraph, 35 U.S.C. § 112, first paragraph, and 35 U.S.C. § 103.

The examiner shall set a time for response to the NEW GROUND OF REJECTION when he sets the time for response to further action under 35 U.S.C. § 112, second paragraph, 35 U.S.C. § 112, first paragraph, and 35 U.S.C. § 103.

This application, by virtue of its "special" status, requires an immediate action. MPEP § 708.01(d). It is important that the Board of Patent Appeals and Interferences be informed promptly of any action affecting the appeal in this case.

AFFIRMED-IN-PART; 37 CFR § 1.196(b); REMANDED

TEDDY S. GRON Administrative Patent Judge	
RICHARD TORCZON Administrative Patent Judge	BOARD OF PATENT APPEALS AND INTERFERENCES
HUBERT C. LORIN Administrative Patent Judge	

bae

Appeal No. 95-3606
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